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Dynamics of glomerular ultrafiltration following open-heart surgery

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Dynamics of glomerular ultrafiltration following open-heart surgery. To elucidate how individual determinants might lower the rate of glomerular ultrafiltration (GFR) in some patients following cardiac surgery, we performed hemodynamic measurements and clearances of inulin (as a measure of GFR), PAH (as a measure of effective renal plasma flow [ERPF]), and dextran-40. Two groups of 17 patients each were distinguished by the presence or absence of prerenal azotemia. Glomerular hypofiltration (GFR = 21 ± 2 vs. 76 ± 6 ml/min/1.73 m^2, $P < 0.001$) in the former was accompanied by depressed left ventricular function, arterial pressure, and ERPF (152 ± 26 vs. 317 ± 32 ml/min/1.73 m^2, $P < 0.001$). To determine if factors beside ERPF play a role in lowering GFR, we calculated the efferent oncotic pressure (π_e). Failure of GFR to change over a 24-hour period despite increases in ERPF suggested that both patient groups were at filtration pressure disequilibrium (FPD). This condition permits calculation of a unique glomerular ultrafiltration coefficient (Kf). Over a range of pressures for transcapillary hydraulic pressure ($\overline{\Delta P}$), such that $3 \leq (\overline{\Delta P} - \pi_e) \leq 10$ mm Hg (to simulate FPD), Kf was less than 0.08 ml · sec^{-1} · mm Hg^{-1} · 1.73 m^{-2} in azotemic, but exceeded this value in nonazotemic patients. Although a selective reduction of Kf is predicted to lower the fractional clearance of dextrans, these were significantly elevated in azotemic relative to nonazotemic patients (molecular radii 30 − 40 Å). A theoretical analysis of the latter data suggests that over the foregoing range of FPD, a 15 to 30% decline in $\overline{\Delta P}$ combined with a 30 to 0% reduction in Kf from values in nonazotemic patients best explains the experimental findings in azotemic patients.

Dynamique de la filtration glomérulaire après chirurgie à coeur ouvert. Afin de savoir comment des déterminants individuels peuvent abaisser le débit de filtration glomérulaire (GFR) chez certains malades après chirurgie cardiaque des mesures hémodynamiques et de clairances de l'inulin (chez GFR), du PAH (chez ERPF) et du dextran-40 ont été réalisées. Deux groupes de 17 malades chacun ont été constitués en fonction de l'absence ou de la présence d'azotémie pré-rénale. Dans le premier groupe la baisse de GFR (21 ± 2 vs. 76 ± 6 ml/min/1,73 m^2, $P <$ 0,001) était accompagnée d'un abaissement de la fonction ventriculaire gauche, de la pression artérielle et de ERPF (152 ± 26 vs. 317 ± 32 ml/min/1,73 m^2, $P < 0{,}001$). Afin de savoir si des fonctions autres que ERPF jouent un rôle dans l'abaissement de GFR la pression oncotique efférente (π_e) a été calculée. Le fait que GFR n'ait pas changé sur une période de 24 heures malgré des augmentations de ERPF suggère que les deux groupes de sujets étaient en situation de déséquilibre en ce qui concerne la pression de filtration (FPD). Cette situation permet de calculer un seul coefficient d'ultrafiltration glomérulaire (Kf). Dans un éventail de valeurs de la pression hydraulique transcapillaire ($\overline{\Delta P}$) tel que $3 \leq (\overline{\Delta P} - \pi_e) \leq 10$ mm Hg (pour stimuler FPD), Kf était inférieur à 0,08 ml · sec^{-1} · mm Hg^{-1} · 1,73 m^2 chez les azotémiques mais était supérieur à cetta valeur chez les malades non azotémiques. Alors qu'une réduction sélective de Kf devrait abaisser la clairance fractionnelle des dextrans, celle-ci était significativement plus grande chez les malades azotémiques (diamètres moléculaires, 30 à 40 Å). Une analyse théorique de ces résultats suggère que dans l'éventail des valeurs de FPD déjà mentionné une dimunition de 15 à 30% de $\overline{\Delta P}$ associée à une réduction de 30% de Kf par rapport aux malades non-azotémiques est la meilleure explication des constatations faites chez les malades azotémiques.

Between 2 and 7% of all patients undergoing open-heart surgery develop acute renal failure (ARF) in the postoperative period [1–5]. This lesion is thought to be hemodynamically mediated and is characterized by a renal excretory failure that is so profound and protracted that it necessitates dialysis therapy in most cases [5, 6]. More common than intrinsic ARF, however, is a transient decline in renal function sufficient to produce postoperative azotemia [1–3]. Studies of patients with this milder lesion have revealed severe depression of the glomerular filtration rate (GFR), sodium retention, and a persisting if somewhat impaired ability to form a concentrated urine [5, 7–9]. Based on these findings, it has generally been regarded that such transient postoperative azotemia represents a form of prerenal failure.

To elucidate the pathogenesis of impaired postoperative renal function, most investigators have focused their attention on the surgical procedure and in particular on the period of cardiopulmonary bypass (CPB) [7, 8, 10–13]. During CPB, the kidneys are generally perfused at a pressure below the autoregulatory range and at a flow below normal (200 to 500 ml/min. [12]). Not surprisingly, GFR declines to low levels. Interpretation of clearance data must, however, be treated with circumspection because of hemodynamic instability, oliguria, and postoliguric washout of clearance markers during CPB [8, 10]. In general, protective measures adopted during surgery, including hypothermia, a low hematocrit perfusate, and intermittent mannitol administration, appear to be effective, and GFR returns toward preoperative control values by the end of surgery [7, 8, 10–13].

Postoperative cardiac performance, on the other hand, clearly an important determinant of renal function, has received relatively little attention. Cardiac functional impairment is

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evident in most patients for one or more days following surgery [14–16], and may be sufficiently severe to account for azotemia of the prerenal type. Although scant information is available for the renal response to poor cardiac function in surgical patients, a large body of data has been amassed in nonsurgical patients with cardiac diseases. Typically, renal vascular resistance rises when the heart fails as a pump, but the rate of glomerular ultrafiltration (GFR) is maintained within the normal range [17, 18], or it declines proportionately less than the fall in effective renal plasma flow (ERPF) [18–22]. This tendency for the filtration fraction to become elevated has generally been observed in patients with well-compensated cardiac failure [17–20, 22]. Not infrequently, however, profound depression of GFR associated with a low filtration fraction has been observed where cardiac output was unusually low [19, 23, 24]. These disparate trends for GFR and ERPF with varying grades of cardiac functional impairment suggest that determinants of glomerular ultrafiltration besides renal plasma flow may become altered. With the successful application of micropuncture techniques to several animal species, it has become apparent that GFR is regulated by four determinants [25, 26]. Three are hemodynamic and include glomerular plasma flow, afferent oncotic pressure (π_a), and the mean hydraulic pressure difference across the glomerular capillary wall ($\overline{\triangle P}$). The remaining determinant, the glomerular ultrafiltration coefficient (Kf), is intrinsic to the glomerular capillary wall and is the product of hydraulic permeability and surface area available for filtration.

To determine whether severe depression of GFR is associated with unusually poor cardiac performance in the early postcardiac operative period, we performed a simultaneous evaluation of the hemodynamic and renal functional status of 34 patients. We then attempted to resolve whether glomerular hypofiltration sufficient to cause azotemia in such patients results solely from changes in some or all of the hemodynamic determinants of GFR and whether alterations of the intrinsic properties of the glomerular capillaries are contributory factors as well.

Methods

Patient population and clinical background. Using a protocol and consent procedure approved by the Committee on the Use of Human Subjects in Research at Stanford University, we selected 34 patients for study. All had undergone open-heart surgery 1 to 4 days previously and had a serum creatinine concentration of less than 2 mg/dl on the day of operation. In 17 patients, serum creatinine was increasing at the time of study, rising from an initial value of 1.5 ± 0.1 mg/dl (mean ± SEM) to a peak value of 3.0 ± 0.7 mg/dl ($P < 0.001$). Corresponding values for blood urea nitrogen concentration were 25 ± 2 and 60 ± 5 mg/dl, respectively. These patients comprise the azotemic (experimental) group. In the remaining 17 patients, serum creatinine concentration was 1.2 ± 0.1 mg/dl on the operation day and remained in the normal range. These latter patients serve as the nonazotemic (control) group. All but three patients in each group were male. Both groups were comprised of patients of moderately advanced age, averaging 67 ± 3 and 58 ± 3 years in azotemic and nonazotemic patients, respectively. Although azotemic patients tended to be older, and to have higher initial serum creatinine levels, neither of these differences from the nonazotemic group reached statistical significance.

Two criteria were used to ensure that azotemic patients did not have ARF at the time of study. One was renal conservation of sodium, defined as a fractional sodium excretion of 1% or less [27]. The second criterion was the absence of transtubular backleak of filtered inulin. Loss of tubular impermeability to inulin is found in experimental animals during the first week of postischemic acute renal failure [28–30], and may be recognized in patients with ARF following open-heart surgery by performing simultaneous clearances of inulin and of larger dextran molecules [6, 31]. These uncharged polysaccharide markers are normally excreted by glomerular filtration and are neither secreted nor reabsorbed [32]. Inulin, which has an Einstein-Stokes radius (ESR) of 13.5 Å, is freely filtered, but restriction to filtration is evident for dextran molecules with an ESR of 22 Å or greater. In patients with postcardiac surgical ARF, however, the clearance of dextran molecules in the ESR range of 22 to 28 Å frequently *exceeds* that of inulin, suggesting that the smaller filtered inulin molecules are leaking back through necrotic tubular epithelium at a more rapid rate than the larger (filtered) dextran molecules do [6, 31]. Sodium-retaining azotemic patients were, therefore, included in the present study only when the dextran-to-inulin clearance ratio was less than unity for dextran molecules of ESR 22 Å and greater, and when this ratio decreased progressively with increasing molecular size. Additional evidence that the renal injury was of a mild nature was afforded by the observation that serum creatinine concentration began to decline spontaneously before the end of the first postoperative week in 14 of the 17 azotemic patients.

Operative and postoperative regimen. As judged by the duration of the cardiopulmonary bypass (CPB), which averaged 161 ± 16 and 140 ± 13 min in azotemic and nonazotemic patients, respectively (P = NS), the magnitude of the surgical procedure was similar in the two groups of patients. The management of patients during CPB, and in the postoperative period, details of which have been published elsewhere [5], was also similar in the two groups of patients. In brief, CPB was achieved with a nonpulsatile system using flow rates between 30 and 50 ml/min/kg and a perfusion pressure averaging 50 mm Hg. Prior to and throughout CPB, all patients were volume expanded with lactated Ringer's solution to which 12.5 g of 20% mannitol was added every 60 min. To maintain a high left atrial filling pressure, we continued the volume expansion in the early postoperative period. As judged by body weight at the time of study, volume expansion averaged 15 and 11% of mean preoperative body weight in azotemic and nonazotemic patients, respectively. In addition, vasodilator therapy with sodium nitroprusside was administered to maintain systemic vascular resistance in the normal range. Fourteen azotemic and thirteen nonazotemic patients also required infusion of the inotropic agent dopamine hydrochloride (6.9 ± 0.9 and 7.9 ± 1.1 μg/kg/min, respectively); and seven azotemic and nine nonazotemic patients received therapy with an intraaortic balloon pump.

Study protocol. All studies were performed when patients were hemodynamically stable. Sudden changes in blood volume, viscosity, and oncotic pressure were prevented by avoiding infusion of packed red cells, hyperoncotic human albumin solution, and diuretics for at least 6 hours prior to study when clinically feasible. During each study, fluid balance was main-

tained by the infusion of isotonic dextrose or saline solution, and the infusion rate of vasoactive drugs remained constant. Radial arterial pressure, monitored via a saline-filled catheter connected to a Hewlett-Packard pressure transducer (model HP 1280), fluctuated by less than 10 mm Hg in all studies.

Cardiac output was determined in duplicate by injection of indocyanine green through a pulmonary arterial catheter, with subsequent analysis by a Waters densitometer (model D-400) and Waters cardiac output computer (model CO-4). The following hemodynamic variables were derived:

Cardiac index (CI) was calculated as

$$CI = CO/BSA \quad (1)$$

where CO is the measured cardiac output in liters/min, and BSA is the body surface area in m^2.

Left ventricular stroke work index (SWI) was determined as

$$SWI = \{[(MAP - LAP) \times SVI] \times (0.0136)\} \quad (2)$$

where MAP is the mean arterial pressure and LAP is the mean left atrial pressure in mm Hg; SVI is the stroke volume index, and SWI is expressed as $g \cdot m/m^2$ from the product of the measured pressure difference and flow, and the factor 0.0136.

Systemic vascular resistance index (SVRI) was calculated as

$$SVRI = (MAP - CVP)/CI \quad (3)$$

where CVP is the central venous pressure in mm Hg, and the resistance index is expressed in Wood units/m^2.

Following a priming injection of inulin (24 mg/kg) paraaminohippurate (3.5 mg/kg) and dextran-40 (130 mg/kg), we administered inulin and PAH at a rate calculated to maintain plasma inulin and PAH concentrations constant at 10 to 15 and 1.0 to 1.5 mg/dl, respectively. After a 60-min equilibration period, three 20-min urine collections were made through an indwelling Foley catheter. Arterial blood was drawn from the radial arterial line to bracket each collection. Clearances of inulin (GFR) and PAH (ERPF) and the fractional excretion of sodium were calculated [6, 31]. Fractional clearances of dextran (Θ_D) were determined from plasma and urine obtained during the first timed collection period, using the equation

$$\Theta_D = (U/P)_D / (U/P)_{In} \quad (4)$$

where $(U/P)_D$ and $(U/P)_{In}$ refer to the urine-to-plasma concentration ratios of dextran and inulin, respectively. Plasma protein concentration and plasma oncotic pressure were determined from the 60-min blood sample.

Determination of the glomerular ultrafiltration coefficient (Kf). Using a mathematical model of glomerular ultrafiltration described previously [33] and developed and verified, in part, by one of us (CRR), an attempt was made to estimate a range of values for the glomerular membrane ultrafiltration coefficient (Kf) in each of the patient groups. To do this, we had to obtain the afferent and efferent arteriolar plasma protein concentrations, C_a and C_e, respectively, the preglomerular plasma flow rate (approximated by PAH clearance), and the average transmembrane (glomerular) hydraulic pressure difference, $\overline{\Delta P}$. C_e was calculated from the filtration fraction (inulin clearance/PAH clearance, FF) and from C_a using the relation:

$$C_e = C_a / (1 - FF) \quad (5)$$

A value for efferent plasma oncotic pressure (π_e) was then derived from C_e using the relation [33]:

$$\pi_e = a_1 C_e + a_2 C_e^2 \quad (6)$$

where $a_1 = 1.629$ mm Hg/g% and $a_2 = 0.2935$ mm Hg/g%.

The correlation was verified for use in man by measuring π with a membrane osmometer over the range of efferent plasma protein concentrations encountered in this study ($6 < C_e < 9$ g/dl). In doing so, it was found that Eq. 6 is accurate to within 2% over this concentration range.

Because $\overline{\Delta P}$ cannot be determined in man, values ranging from $0.1 \leq (\overline{\Delta P} - \pi_e) \leq 10$ mm Hg were examined for each experimental group. The lower bound for $\overline{\Delta P}$ was chosen to approximate conditions of filtration pressure equilibrium, that is, when $\overline{\Delta P}$ and the opposing intraglomerular oncotic pressure become equal at some point in the glomerular capillary network proximal to its efferent end. Filtration pressure equilibrium is typical of species such as the Munich-Wistar rat and squirrel monkey in which glomerular plasma flow is normally less than 160 nl/min [34, 35]. In the human kidney containing two million glomeruli, ERPF averages 600 ml/min [36]. Average glomerular plasma flow, therefore, is high, averaging 300 nl/min. At similarly high glomerular plasma flows in the dog, filtration pressure equilibrium is not achieved and $\overline{\Delta P}$ exceeds oncotic pressure at the efferent end of the glomerular capillary network by 7 to 12 mm Hg [37–39]. The upper bound for $\overline{\Delta P}$ in this study was accordingly selected to match the level of canine filtration pressure disequilibrium.

Renal plasma flow may be profoundly depressed in the presence of a low cardiac output state and might fall into a range consistent with the attainment of filtration pressure equilibrium. If, however, severe depression of ERPF is also accompanied by a decline in Kf, filtration pressure equilibrium might not be achieved [26]. In the aforementioned mammalian species, filtration pressure equilibrium is associated with a striking degree of dependence of GFR on renal plasma flow. We therefore assessed the presence of filtration pressure equilibrium by measuring the change in GFR in response to spontaneous alterations of ERPF. Accordingly, inulin and PAH clearances were repeated 24 hours after the initial study in 7 patients from each group.

Laboratory methods. For the calculation of GFR, inulin concentration in urine and plasma was determined using the autoanalyzer method of Fjeldbo and Stamey [40]. This method uses the fructose-specific reagent resorcinol, which is influenced by the presence of dextran. The autoanalyzer method of Harvey and Brothers was used for the determination of PAH [41].

Separation of dextran-40 and inulin in plasma and urine into narrow fractions (approximately 2 Å) was accomplished by gel permeation chromatography with Sephacryl S200. Two columns, 91 and 95 cm in length with internal diameters of 1.6 cm, were used. Each column was calibrated with three narrow dextran fractions of known molecular size (Pharmacia Fine Chemicals AB, Uppsala, Sweden). Using 0.3% buffered saline as eluent, we collected eluted fractions of 2.6 ml each, with an automatic fractionator (Gilson model S-80). The void volume (V_o) was determined with Blue Dextran, and the fractional volume available to the solute (K_{av}) was calculated as

Table 1. Postoperative hemodynamic and clearance data[a]

	Nonazotemic group (N = 17)	Azotemic group (N = 17)	P
SVRI, *Wood units/m²*	26.2 ± 2.0	25.8 ± 2.7	NS
CI, *liters/min/m²*	2.78 ± 0.16	2.46 ± 0.18	NS
SWI, *g · m/m²*	27.8 ± 2.9	14.4 ± 1.5	<0.001
LAP, *mm Hg*	20 ± 2	27 ± 2	<0.01
MAP, *mm Hg*	87 ± 4	76 ± 2	<0.02
Heart rate, *beats/min*	95 ± 2	98 ± 3	NS
FE_{Na}, *%*	1.0 ± 0.3	0.4 ± 0.1	<0.05
Volume expansion, *%*	10.5 ± 1.4	15.3 ± 2.0	<0.02
ERPF, *ml/min/1.73 m²*	317 ± 32	152 ± 26	<0.001
GFR, *ml/min/1.73 m²*	76 ± 6	21 ± 2	<0.001
Filtration fraction	0.25 ± 0.02	0.16 ± 0.02	<0.001
π_a, *mm Hg*	20.8 ± 0.5	21.4 ± 0.7	NS
π_e, *mm Hg*	33.0 ± 0.9	28.7 ± 1.3	<0.02

[a] Values are expressed as mean ± SEM. SVRI is systemic vascular resistance index; CI, cardiac index; SWI, left ventricular stroke work index; LAP, left atrial pressure; MAP, mean arterial pressure; ERPF, effective renal plasma flow; π_a and π_e, afferent and efferent arteriolar oncotic pressure.

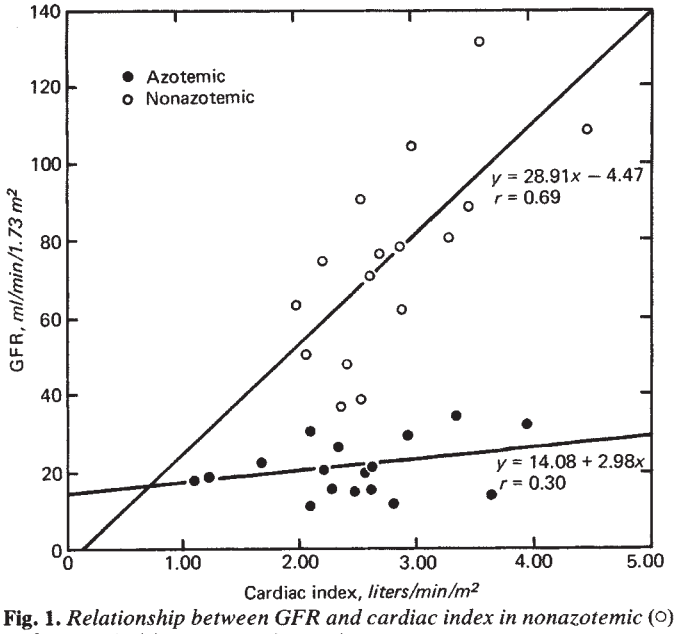

Fig. 1. *Relationship between GFR and cardiac index in nonazotemic* (○) *and azotemic* (●) *postoperative patients.*

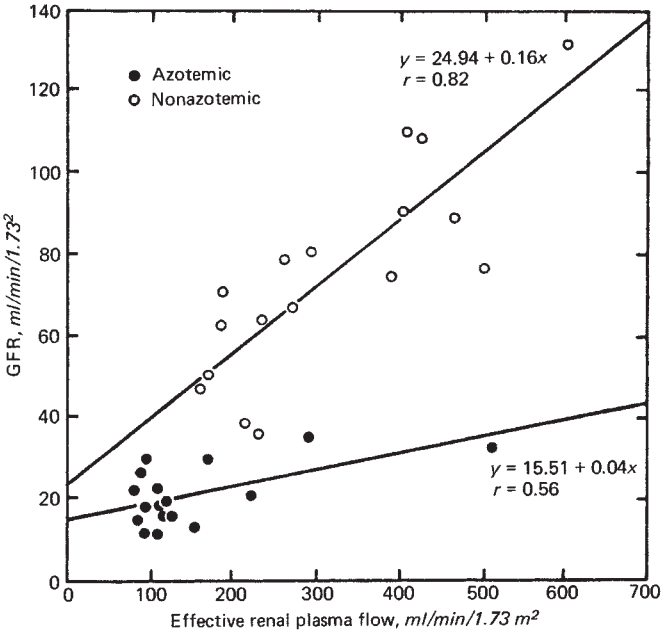

Fig. 2. *Relationship between GFR and effective renal plasma flow in nonazotemic* (○) *and azotemic* (●) *postoperative patients.*

$$K_{av} = (V_e - V_o)/(V_t - V_o) \quad (7)$$

where V_e is the elution volume of the solute and V_t the total volume of the gel column [42]. Einstein-Stokes radii (ESR) for individual dextran fractions were calculated from K_{av} [43].

Following gel-permeation chromatography of plasma and urine, eluted fractions were assayed for dextran and inulin concentrations using a modification of the autoanalyzer anthrone method of Scott and Melvin [44]. Plasma oncotic pressure was determined with an IL 186 Weil oncometer, and plasma total protein concentration with a standard Biuret technique.

Statistical methods. Data for each patient group were analyzed by means of the Statistical Package for the Social Sciences [45]. A two-tailed student's t test with separate variance estimates was used to test the significance of the differences observed. To determine the significance of change in clearance values over time, we performed statistical comparison to the first study using a two-tailed t test for paired data (SPSS) [45]. All results are expressed as the mean and the SEM.

Results

Hemodynamic findings (Table 1). The hemodynamic findings for each of the two patient groups are summarized in Table 1. Systemic vascular resistance was successfully lowered into the normal range by sodium nitroprusside in both patient groups, averaging 26.2 ± 2.0 and 25.8 ± 2.7 Wood units/m² in nonazotemic and azotemic patients, respectively. Volume expansion

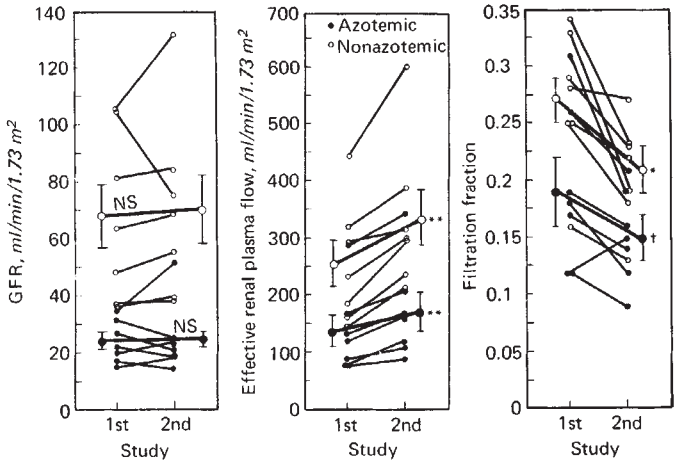

Fig. 3. *Effects on GFR* (left panel) *of spontaneous increases in effective renal plasma flow* (middle panel), *in nonazotemic* (○) *and azotemic* (●) *postoperative patients.* Change in filtration fraction is illustrated in right panel. † = $P < 0.1$, * = $P < 0.05$, ** = $P < 0.005$, NS = not significant.

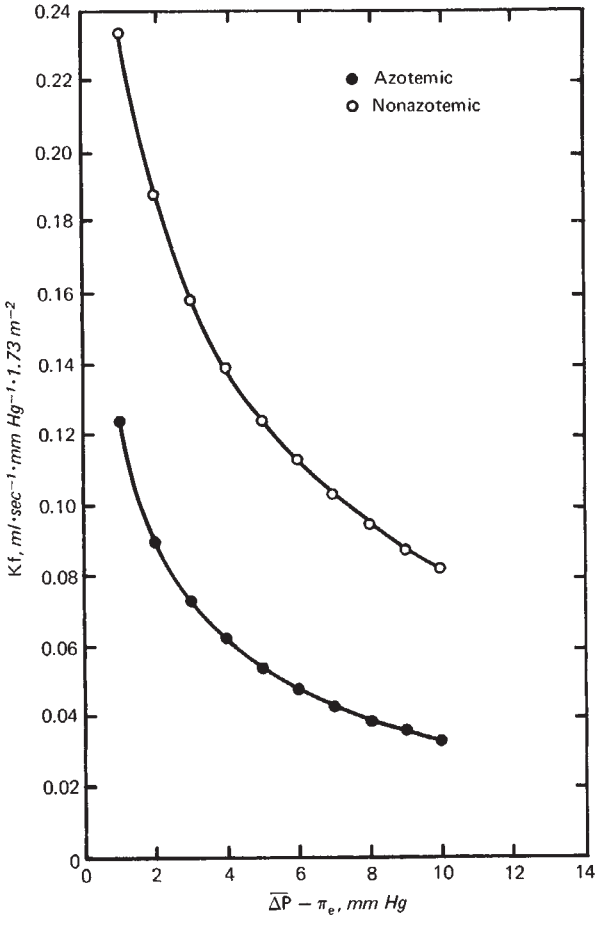

Fig. 4. *Calculated glomerular ultrafiltration coefficient (Kf) for values of mean transcapillary hydraulic pressure difference ($\overline{\Delta P}$) exceeding efferent oncotic pressure (π_e) by 1 to 10 mm Hg.* In nonazotemic patients, indicated by an *open circle* (○), absolute values for $\overline{\Delta P}$ vary from 34 to 43 mm Hg. In azotemic patients, indicated by a *closed circle* (●), absolute values for $\overline{\Delta P}$ vary from 30 to 39 mm Hg.

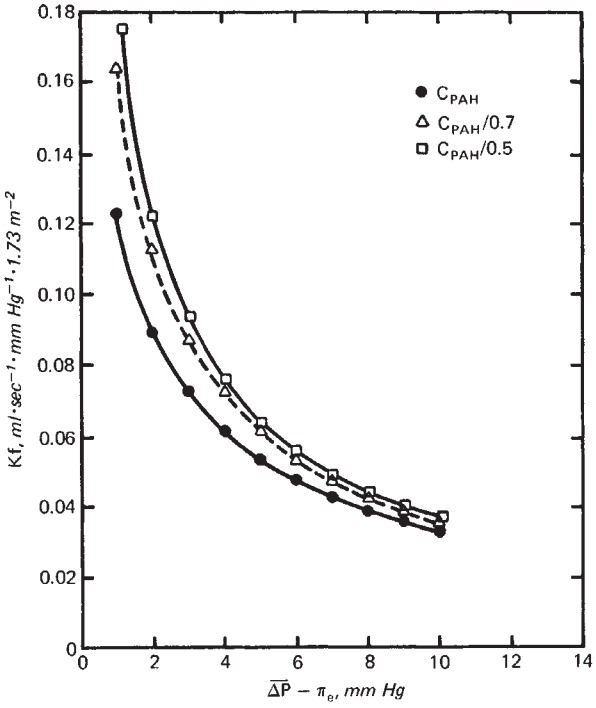

Fig. 5. *Theoretical analysis of the effects of a reduction in PAH extraction on the glomerular ultrafiltration coefficient in azotemic patients.* The lower curve was calculated using PAH clearance as a measure of renal plasma flow. For the middle and upper curves, renal plasma flow was calculated assuming a PAH extraction ratio of 0.7 and 0.5, respectively.

resulted in a high left ventricular filling pressure, which, as judged by mean pulmonary arterial diastolic pressure, was significantly higher in the azotemic group (27 ± 2 mm Hg) than in the nonazotemic group (20 ± 2 mm Hg, $P < 0.01$). Notwithstanding this successful manipulation of cardiac preload and afterload, nonazotemic patients still manifested a mild low cardiac output state, as judged by a cardiac index of 2.78 ± 0.16 liters/min/m^2 on the average (normal, 2.8 to 4.2 liters/min/m^2 [46]). Similarly, a mean left ventricular stroke work index of 27.8 ± 2.9 g · m/m^2 (normal, 30 to 100 g · m/m^2 [46]) reflects depression of the left ventricular function curve. By comparison, profound depression of cardiac function and a severe low cardiac output state characterized azotemic patients. Cardiac index was depressed to 2.46 ± 0.18 liters/min/m^2, and left ventricular stroke work index was extremely depressed to 14.4 ± 1.5 g · m/m^2, a value lower than that in nonazotemic patients ($P < 0.001$).

Mean arterial pressure averaged 87 ± 4 mm Hg in nonazotemic patients, but was at the lower end of the autoregulatory range in azotemic patients, averaging 76 ± 2 mm Hg ($P < 0.02$). The renal hemodynamic response in each group was characterized by a depression of ERPF and a blunting of urinary sodium excretion. Effective renal plasma flow was more depressed in azotemic than it was in nonazotemic patients, averaging 152 ± 26 vs. 317 ± 32 ml/min/1.73 m^2 ($P < 0.001$). Notwithstanding volume expansion, which resulted in a weight gain of 11 ± 1% in nonazotemic patients and 15 ± 2% in azotemic patients,

Table 2. Fractional dextran clearances[a]

	Einstein-Stokes radius, Å													
	20	22	24	26	28	30	32	34	36	38	40	42	44	46
Nonazotemic group (N = 17)	0.99 ±0.03	0.94 ±0.03	0.87 ±0.03	0.81 ±0.03	0.73 ±0.03	0.65 ±0.03	0.55 ±0.03	0.45 ±0.02	0.35 ±0.02	0.29 ±0.02	0.22 ±0.02	0.17 ±0.02	0.12 ±0.01	0.09 ±0.01
Azotemic group (N = 17)	0.99 ±0.02	0.95 ±0.02	0.90 ±0.02	0.89 ±0.04	0.81 ±0.03	0.74 ±0.03	0.67 ±0.03	0.57 ±0.03	0.46 ±0.03	0.37 ±0.02	0.29 ±0.02	0.21 ±0.02	0.15 ±0.01	0.11 ±0.01
P	NS	NS	NS	NS	NS	<0.05	<0.01	<0.005	<0.005	<0.01	<0.02	NS	<0.05	NS

[a] Values are the means ± SEM.

fractional sodium excretion averaged only 1.0 ± 0.3 and 0.4 ± 0.1% ($P < 0.05$), respectively.

Dynamics and determinants of glomerular ultrafiltration (Table 1, Figs. 1–4). The GFR varied widely in nonazotemic patients, ranging from 37 to 132 ml/min/1.73 m^2. The mean value of 76 ± 6 ml/min/1.73 m^2 was significantly higher than that in azotemic subjects in whom GFR averaged 21 ± 2 ml/min/1.73 m^2 ($P < 0.001$). Similarly, the filtration fraction was higher in the nonazotemic group, averaging 0.25 ± 0.02 vs. 0.16 ± 0.02 in azotemic patients ($P < 0.001$). Given the higher filtration fraction and a value for π_a that was not different from that in the azotemic group (20.8 ± 0.5 vs. 21.4 ± 0.7 mm Hg, respectively), the calculated value for mean π_e of 33.0 ± 0.9 mm Hg in nonazotemic patients was significantly elevated above that in azotemic patients (28.7 ± 1.3 mm Hg, $P < 0.02$).

The GFR appeared to reflect the hemodynamic status of nonazotemic patients. As shown in Figs. 1 and 2, GFR was highly correlated with cardiac index ($r = 0.69$, $P < 0.002$) and ERPF ($r = 0.82$, $P < 0.001$). In contrast, there was no correlation between GFR and cardiac index in azotemic patients ($r = 0.30$, P = NS), and GFR was less well correlated with ERPF ($r = 0.56$, $P < 0.01$) than it was in nonazotemic patients. Despite the significant correlation between GFR and ERPF in both patient groups, GFR was not highly plasma-flow dependent. In 14 patients who were reexamined 24 hours after the initial study, ERPF had increased uniformly whereas, with one exception, GFR increased proportionately less or actually declined. In 7 nonazotemic patients, ERPF increased by 32% from 254 ± 40 to 336 ± 49 ml/min/1.73 m^2 ($P < 0.005$). Similarly, ERPF in 7 azotemic patients increased by 23% from 138 ± 28 to 170 ± 33 ml/min/1.73 m^2 ($P < 0.005$). In contrast, the mean GFR remained unchanged (68 ± 4 and 70 ± 12 ml/min/1.73 m^2 in nonazotemic patients and 24 ± 3 and 25 ± 5 ml/min/1.73 m^2 in azotemic patients). The failure of GFR to increase in proportion to ERPF is reflected by a 23% and 15% reduction in filtration fraction in nonazotemic and azotemic patients, respectively (Fig. 3).

The results of Kf over a range of values 1 mm Hg $\leq (\overline{\Delta P} - \pi_e) \leq$ 10 mm Hg are illustrated in Fig. 4. Over this entire range in nonazotemic patients ($\overline{\Delta P}$ = 34 to 43 mm Hg), Kf never fell below 0.08 ml · sec^{-1} · mm Hg^{-1} · 1.73 m^2. In contrast, Kf exceeded 0.08 ml · sec^{-1} · mm Hg^{-1} · 1.73 m^2 in azotemic patients with severe cardiac failure only when $\overline{\Delta P}$ was within 2 mm Hg of π_e. Given the poor correlation between GFR and ERPF, and the failure of GFR to rise in response to spontaneous increases in ERPF, it seems likely that, despite severe reduction in ERPF, these latter patients were not at or close to filtration pressure equilibrium. It is important to note, therefore, that for values of 3 mm Hg $\leq (\overline{\Delta P} - \pi_e) \leq$ 10 mm Hg (that is, $\overline{\Delta P}$ = 32 to 39 mm Hg), Kf in azotemic patients fell substantially below 0.08 ml · sec^{-1} · mm Hg^{-1} · 1.73 m^{-2}.

Many of the input values in our ultrafiltration model are derived from the rate of renal plasma flow, which was determined from the clearance of PAH. Because the ability of the proximal tubule cell to secrete PAH may become impaired in the presence of severe renal ischemia, we have examined the effects of reduced PAH extraction on the computed values for Kf in the azotemic patient group. The results of these computations are compared with those obtained with PAH clearance (lower curve) in Fig. 5. As shown, an assumed reduction of the PAH extraction ratio to 0.7 or 0.5 with appropriate correction of the rate of renal plasma flow, has relatively little effect on the calculated value for Kf. This is particularly true over the range of $\overline{\Delta P}$ values consistent with filtration pressure disequilibrium (3 mm Hg $\leq [\overline{\Delta P} - \pi_e] \leq$ 10 mm Hg) in which Kf remains below 0.08 ml · sec^{-1} · mm Hg^{-1} · 1.73 m^{-2}, even when the PAH extraction ratio is reduced to 0.5.

Urinary dextran clearances (Table 2, Fig. 6). The fractional clearance values for dextrans relative to inulin (Θ_D) in each patient group are plotted as a function of ESR in Fig. 6. Measurable restriction to dextran (indicated by Θ_D<1) occurred when ESR > ~22 Å. With increasing molecular size, Θ_D declined and approached a value of 0.10 for dextrans with an ESR of 46 Å. The values for Θ_D in nonazotemic patients were similar to those reported by us previously for healthy adult volunteers [31]. For molecules of equivalent size, Θ_D tended to be elevated in azotemic relative to nonazotemic patients. This elevation was highly significant and most striking (27 to 32%) over the ESR range 32 to 40 Å (Table 2). For molecules of smaller or larger size, the elevation of Θ_D in azotemic relative to nonazotemic patients was less than 20% and in most instances failed to achieve statistical significance.

Discussion

The rate of glomerular ultrafiltration in patients who did not become azotemic following cardiac surgery was highly correlated with cardiac performance (Fig. 1). Under the conditions of moderate cardiac functional impairment that obtained in these patients, GFR was in or close to the range expected for normal subjects of this age. As judged by a filtration fraction of 0.25 ± 0.02, which is higher than that found in normal subjects (0.18 to 0.20 [47]), GFR declined proportionally less than ERPF did. A similar response has been documented in patients with stable valvular heart disease [17–19, 21, 22] and has been attributed to

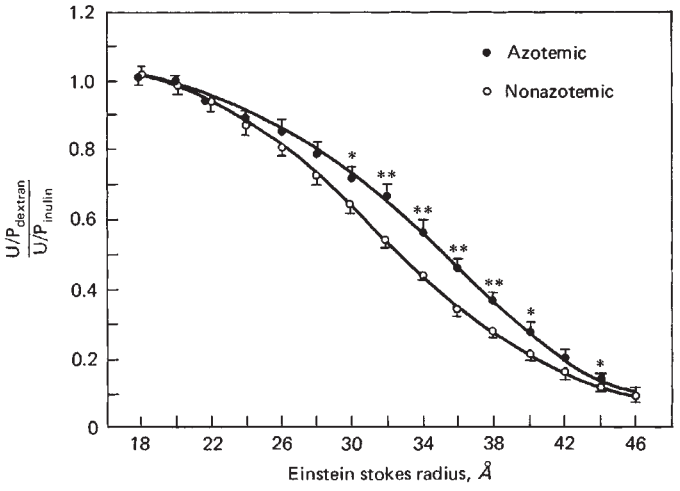

Fig. 6. *Fractional dextran clearance profiles in nonazotemic (○) and azotemic (●) postoperative patients.* Results are expressed as the means ± SEM. * = $P < 0.05$; ** = $P < 0.005$.

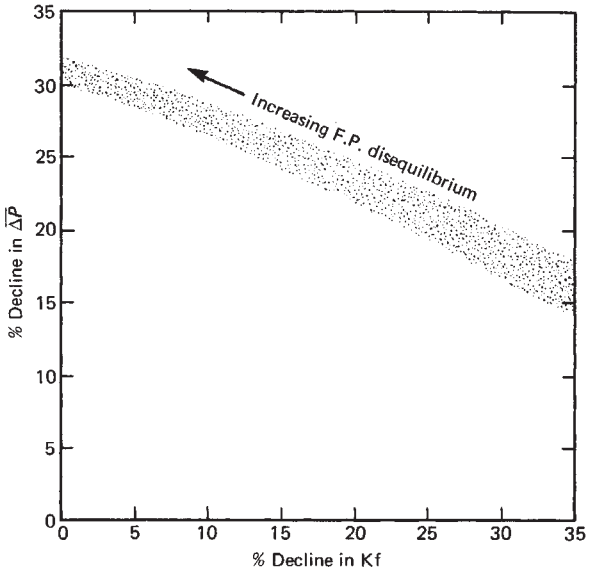

Fig. 7. *Percent reduction in $\overline{\Delta P}$ and Kf from values in nonazotemic patients required to elevate the fractional dextran clearance profile to levels observed in azotemic patients at the measured values of ERPF and π_a in the latter group.* The *stippled zone* incorporates the percent declines for $\overline{\Delta P}$ and Kf needed for selected values of $\overline{\Delta P}$ in nonazotemic patients between 35 (*right-hand side*) and 46 mm Hg (*left-hand side*), respectively. F.P. denotes filtration pressure.

a compensatory increase in glomerular ultrafiltration pressure [48]. Assuming that ERPF was equally distributed among all two million glomeruli in each patient, mean glomerular plasma flow would approximate 160 nl/min, a flow rate at which filtration pressure equilibrium is unlikely to be achieved [25, 26, 38]. Indirect evidence that filtration pressure disequilibrium obtained in these patients is provided by the failure of GFR to increase in proportion to spontaneous increases in ERPF (Fig. 3) It is interesting to note, therefore, that an assigned range of values for $\overline{\Delta P}$ in excess of π_e by 3 to 10 mm Hg (or $\overline{\Delta P}$ = 36 to 43 mm Hg) yielded a value for Kf of between 0.08 and 0.16 ml · sec^{-1} · mm Hg^{-1} · 1.73 m^2 (Fig. 4). This range of values corresponds to an average Kf per glomerulus of 0.04 to 0.08 nl · sec · mm Hg^{-1} and is quite similar to that obtained by more direct methods in all mammalian species examined to date [26, 35, 37, 49].

By contrast, cardiac performance and GFR were poorly correlated in azotemic patients. The severe low cardiac output state was accompanied by depression of GFR to a value, 21 ± 2 ml/min/1.73 m^2, corresponding to only 28% of that in nonazotemic controls. In attempting to elucidate the mechanism of the profound glomerular hypofiltration observed in these patients, it is useful to consider the relative contribution of each of the determinants of GFR.

As judged by PAH clearance, ERPF, an important determinant of GFR [25], was depressed to 48% of that in nonazotemic controls. Reduced renal plasma flow, therefore, presumably played a role in lowering GFR. It could be argued that the severe renal ischemia observed in azotemic patients might impair PAH extraction by the kidney, and that PAH clearance may, in fact, provide an underestimate of ERPF. Earlier studies of patients with low cardiac output states, however, have invariably demonstrated PAH extraction to be normal despite significant elevation of renal vascular resistance [18–20, 22]. Nevertheless, because no attempt was made by us to directly estimate PAH extraction in these critically ill patients, we cannot exclude the possibility that ERPF may have been higher than suggested by the PAH clearance. It is important to point out, therefore, that in such an event, the value of filtration fraction in azotemic subjects would be even lower than the 0.16, suggested by the inulin-to-PAH clearance ratio, and below that found in normal subjects [47]. Under the conditions of filtration pressure disequilibrium, which appear to have obtained in these patients (Fig. 3), had values for the remaining determinants of GFR been the same as those in nonazotemic controls, a selective reduction in ERPF would be predicted to result in a higher and not a lower filtration fraction [25]. One or more of the remaining determinants of GFR must therefore have changed simultaneously with the depression of ERPF.

Afferent oncotic pressure in this study was measured directly with a membrane osmometer. The average value of 21 mm Hg is similar to that reported by Weil et al for normal subjects at bedrest [50]. More importantly, π_a was not different between the two patient groups and cannot be invoked, therefore, to explain the observed differences in GFR and filtration fraction. By exclusion, these differences appear to be attributable to reductions in either $\overline{\Delta P}$ or Kf alone, or in some combination thereof. Such reduction in either $\overline{\Delta P}$ and/or Kf must be consistent with the measured urinary fractional dextran clearances shown in Fig. 6, in particular, the elevated fractional clearances seen in azotemic relative to nonazotemic patients.

It is recognized that transcapillary solute exchange in the renal glomerulus is governed, in part, by the same determinants that control the ultrafiltration process, namely, $\overline{\Delta P}$, ERPF, π_a, and Kf [51, 52]. For neutral solutes, membrane permselectivity is also dependent on molecular size and shape as well as on an intrinsic membrane transport parameter (for example, pore size or pore density) [51]. Because glomerular morphology remains unaltered in the presence of cardiac failure [53, 54], we assumed that pore size remains unchanged in the two patient popula-

tions. We then used a theoretical model of transcapillary solute exchange based on a hydrodynamic theory of transport of neutral macromolecules through an uncharged isoporous membrane [51]. From this theoretical model, it is possible to compute the magnitude of the reductions in $\overline{\Delta P}$ and Kf, which are consistent not only with the measured values of ERPF and π_a, but also with the fractional clearance profiles for neutral dextran shown in Fig. 6. The results of such computations are presented in Fig. 7, which shows the percent declines in $\overline{\Delta P}$ and Kf needed to elevate the fractional dextran clearance profile from the mean of that observed in the nonazotemic patients to the mean ± 1 SEM of that observed in the azotemic patients. Although inferred but not explicitly indicated in Fig. 7, reductions in Kf alone cannot account for the elevation in Θ_D seen in azotemic patients relative to the nonazotemic group. Indeed, reductions in Kf without concomitant reductions in $\overline{\Delta P}$ always result in a lowering of Θ_D, not an elevation of Θ_D as was observed. In contrast, a selective reduction by 30% of ΔP from values of approximately 46 mm Hg (that is, $\overline{\Delta P} - \pi_e = \sim 13$ mm Hg) with essentially no change in Kf would be consistent with the observations. As shown in Fig. 7, smaller reductions in ΔP from values within 5 mm Hg of filtration pressure equilibrium require, at most, a concomitant 30% reduction in Kf. Because GFR in azotemic patients was not sensitive to changes in ERPF, it may be inferred that these patients were not at filtration pressure equilibrium and that the values at the right hand extreme of the calculated zone are unlikely to have obtained (that is, percent declines in Kf exceeding approximately 30%). Put another way, the observed increase in the fractional clearances of dextrans in azotemic patients seems to be best explained by a reduction of $\overline{\Delta P}$ to a value between 30 and 15% below that in nonazotemic patients with a corresponding reduction in the value for Kf of between 0 and 30%, respectively. The greater the degree of filtration pressure disequilibrium obtaining, the larger is the contribution of $\overline{\Delta P}$ relative to Kf reduction.

Although our findings are of necessity based on an indirect approach and are not entirely conclusive, we would suggest that GFR in the postoperative period following open-heart surgery is a function of cardiac performance. When impairment of cardiac performance is moderate, as in our nonazotemic patients, GFR falls less than in proportion to ERPF, possibly as a result of a compensatory increase in $\overline{\Delta P}$. Below some critical level of cardiac function, as in our azotemic patients, this compensatory mechanism fails, and GFR and filtration fraction become severely reduced. A reduction in $\overline{\Delta P}$, probably in combination with reduced Kf, appears to lower GFR disproportionately to the accompanying depression of ERPF.

Direct measurements in the normal Munich-Wistar rat have revealed that at arterial pressures above 90 mm Hg, $\overline{\Delta P}$ (like renal blood flow) is autoregulated by a resetting of the resistances in afferent and efferent arterioles [55]. At values of arterial pressure below 90 mm Hg, however, $\overline{\Delta P}$ has been shown to decline in both the rat and the dog [38, 55]. In keeping with these findings, it may be that $\overline{\Delta P}$ in azotemic patients declined as a consequence of the relative arterial hypotension associated with the low cardiac output state (MAP = 76 ± 2 mm Hg, Table 1). Inasmuch as arterial hypotension may be attributed in part to the use of sodium nitroprusside infusion in these patients, the role of aggressive afterload reduction in low output cardiac failure merits review. It may be that the advantage of increasing cardiac output by this technique is offset by a profound decline in GFR when arterial pressure is allowed to fall below the autoregulatory range. We suggest that under such circumstances it would be prudent to monitor GFR while permitting arterial pressure to rise by reducing or withholding the infusion of vasodilator agents.

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